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DOPAMINERGIC 2-AMINOTETRALINS

Synthesis, Conformational Analysis, and Structure-Activity Relationships

by

Anette M. Johansson

UPPSALA 1987

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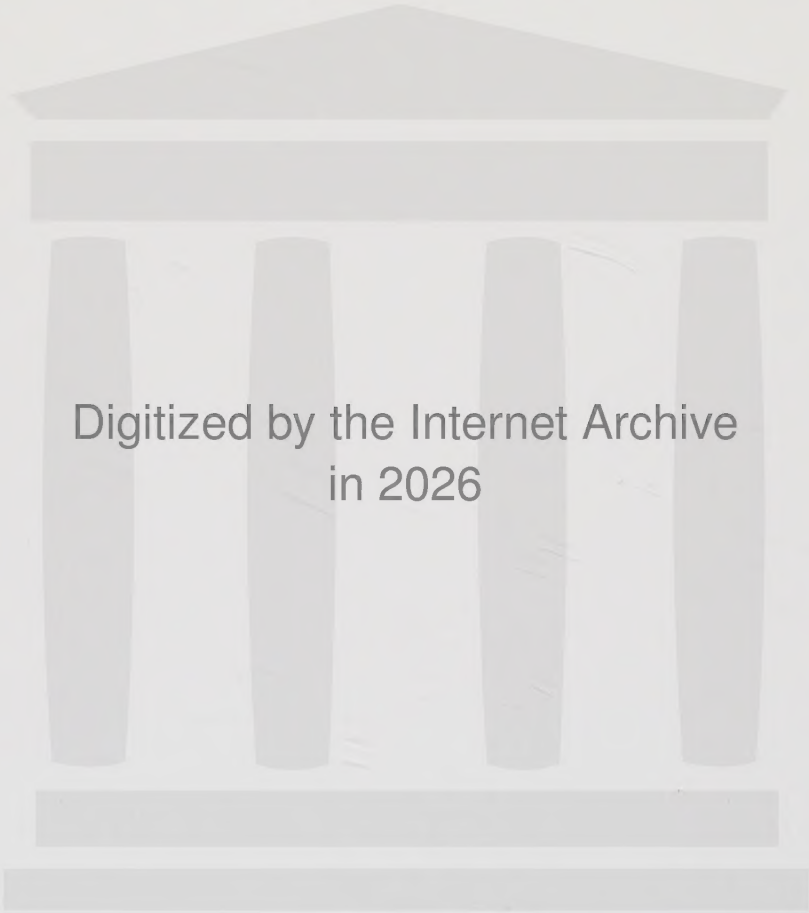
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ABSTRACT

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Methyl substituted derivatives of the potent dopamine (DA) D_2-receptor agonists 5- and 7-hydroxy-2-(di-n-propylamino)tetralin (5-OH-DPAT and 7-OH-DPAT) have been synthesized and evaluated for central DA receptor activity by use of in vivo and in vitro pharmacological tests. Compounds with novel pharmacological profiles of potential clinical value have been discovered.

Conformational analysis of some compounds by use of x-ray crystallography, ^1H- and ^{13}C NMR spectroscopy, and molecular mechanics (MMP2) calculations have been made in attempt to correlate pharmacological effects with the conformational preferences. A hypothesis have been put forward about the "DA D_2-receptor active conformations" of 2-amino-5-hydroxytetralins and 2-amino7-hydroxytetralins, respectively. A partial "DA D_2-receptor excluded volume have been defined.

New synthetic pathways for 5-, 7-, and 8-methoxy-3-methyl-2-tetralones have been developed.

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1 PAPERS DISCUSSED

This thesis is based on the following papers, which are referred to by the Roman numerals I-VIII in the text.

I C_1-Methylated 5-Hydroxy-2-(dipropylamino)tetralins - Central Dopamine-Receptor Stimulating Activity.
U. Hacksell, A.M. Johansson, L.-E. Arvidsson, J.L.G. Nilsson, S. Hjorth, K. Svensson, A. Carlsson, H. Wikström, D. Sanchez, P. Lindberg.
J. Med. Chem., 27, 1003, (1984).

II Novel Dopamine Receptor Agonists and Antagonists with Preferential Action on Autoreceptors.
A.M. Johansson, L.-E. Arvidsson, U. Hacksell, J.L.G. Nilsson, K. Svensson, S. Hjorth, D. Clark, A. Carlsson, D. Sanchez, B. Andersson, H. Wikström.
J. Med. Chem., 28, 1049, (1985).

III Resolved cis- and trans-2-Amino-5-methoxy-1-methyltetralins: Central Dopamine Receptor Agonists and Antagonists.
A.M. Johansson, L.-E. Arvidsson, U. Hacksell, J.L.G. Nilsson, K. Svensson, A. Carlsson.
J. Med. Chem. In press.

IV Dopaminergic 2-Aminotetralins: Affinities for Dopamine D_2-Receptors, Molecular Structures, and Conformational Preferences.
A.M. Johansson, A. Karlén, C.J. Grol, S. Sundell, L. Kenne, U. Hacksell.
Mol. Pharmacol. 30, 258, (1986).

V C3-Methylated 5-Hydroxy-2-(dipropylamino)tetralins: Conformational and Steric Parameters of Importance for Central Dopamine Receptor Activation.
A.M. Johansson, J.L.G. Nilsson, A. Karlén, U. Hacksell, K. Svensson, A. Carlsson, L. Kenne, S. Sundell.
Submitted for publication in J. Med. Chem.

VI C1- and C3-Methyl Substituted Derivatives of 7-Hydroxy-2-(dipropylamino)tetralin (7-OH-DPAT): Activities at Central Dopamine Receptors.
A.M. Johansson, J.L.G. Nilsson, A. Karlén, U. Hacksell, D. Sanchez, K. Svensson, S. Hjorth, A. Carlsson, L. Kenne, S. Sundell.
In manuscript.

VII Facile Synthesis of 5-Methoxy-3-methyl-2-tetralone.
J.R.M. Lundkvist, A.M. Johansson, L.-E. Arvidsson, U. Hacksell.
Acta Chem. Scand. Ser.B, 40, 508, (1986).

VIII Syntheses of 5-, 7- and 8-Methoxy-3-methyl-2-tetralones.
A.M. Johansson, C. Mellin, U. Hacksell.
J. Org. Chem., In press.

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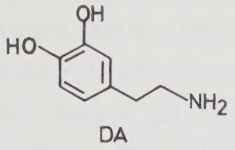
2 GENERAL INTRODUCTION

2.1 Clinical potential of dopamine (DA) receptor agonists

Disturbances in central dopamine (DA) transmission [1-3] are supposed to be involved in Parkinson's disease and schizophrenia.



DA

The role of DA in Parkinson's disease can be regarded as established. There is evidence for a degeneration of the DA neurons in the nigrostriatal system [3]. The disease is characterized by motor disturbances such as hypokinesia, muscular rigidity, and tremor [4]. Today dopaminergic [5,6] or anticholinergic drugs are used in the treatment of Parkinson's disease.

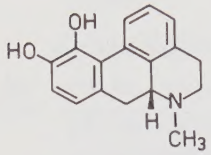
The antipsychotic action of DA receptor antagonists and the similarity between paranoid schizophrenia and amphetamine induced psychoses has resulted in the "DA-hypothesis of schizophrenia". This hypothesis suggests that schizophrenia involves an excess of DA neuronal activity in the central nervous system (CNS) [1,2,7]. The finding that activation of DA autoreceptors decreases the activity in the DA neurons, has initiated a search for selective DA autoreceptor agonists, since such drugs are of potential use as antipsychotic agents.

Other potential therapeutic indications of DA receptor agonists include hyperprolactinemia, acromegaly, certain pituitary tumors and shock (for reviews, see refs. 8 and 9).

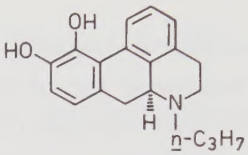
2.2 Apomorphine

The DA receptor agonist (-)-apomorphine (usually named apomorphine) was first synthesized in 1896 by an acid

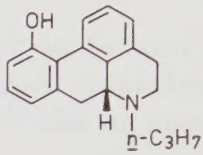
catalyzed rearrangement of naturally occurring morphine [10]. The absolute configuration at the asymmetric carbon 6a has been determined to be R [11-14]. The early interest in and use of (R)-apomorphine was as an emetic agent. First in 1950 Schwab et al. [15] showed that (R)-apomorphine had an ameliorative effect in Parkinson's disease. Although the emetic effect, the low oral bioavailability, and the short duration of action make (R)-apomorphine less useful clinically, it has been widely used to evaluate DA function in man [16-23].



(R)-Apomorphine



(S)-NPA



(R)-11-OH-NPA

Racemic apomorphine was synthesized in 1970 [24] and resolution gave the (S)-enantiomer [25]. (S)-Apomorphine was first considered to be devoid of dopaminergic activity. However, recent findings indicate that (S)-apomorphine has an antagonistic effect at DA receptors [26-32].

Several derivatives of apomorphine have been synthesized. Structure-activity relationship (SAR) studies reveal that the potent DA receptor agonists, which are structurally related to (R)-apomorphine, are homochiral (homochiral compounds have the same sense of chirality but not necessarily the same absolute configuration) with (R)-apomorphine [33,34]. In addition, the hydroxyl group in the 11-position of the aporphine ring, corresponding to the meta-OH in DA, seems to be important for agonist activity. Furthermore, O-methylation reduces activity, and the effects of variation of the N-substituent seem to be complex [33,34]. (R)-10,11-Dihydroxy-N-n-propylnorapomorphine [(R)-NPA] [33-38] and (R)-11-hydroxy-N-n-propylnorapomorphine [(R)-11-OH-NPA] [33,34,39] are two potent DA receptor

agonists. (S)-NPA was recently shown to have anti-dopaminergic effects [29,30,32].

2.3 Structure-activity relationships of dopaminergic 2-aminotetralins

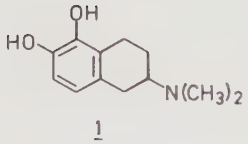
Several comprehensive reviews of structure-activity relationship (SAR) of DA receptor agonists have been published recently [40-42]. The 2-aminotetralin skeleton is a fragment of the apomorphine molecule and it also contains the DA structure. The report in 1972 by Cannon et al. [43] on the potent dopaminergic activity of 1 ("M7") initiated synthesis, pharmacological evaluation and SAR-studies of a large number of closely related 2-aminotetralins. This section will give a brief summary of the SAR of dopaminergic 2-aminotetralins and related compounds.

2.3.1 Substitution at the aromatic ring

The dopaminergic effects of hydroxy substituted 2-(di-n-propylamino)tetralins (DPAT) will be summarized in this section.

The catechols 2 [44-49] and 3 [45,47,50] with hydroxyl groups in the 5,6- and 6,7- positions, have been shown to be potent dopaminergic compounds, whereas 7,8-dihydroxylation gave a compound (4) of lower potency [44]. Only weak dopaminergic effects have been demonstrated after the administration of 5,7- [51] and 5,8- [52] dihydroxylated isomers (5 and 6).

The dopaminergic potency of the monophenolic 2-(di-n-propylamino)tetralins is in the order 5-OH-DPAT > 7-OH-DPAT > 6-OH-DPAT > 8-OH-DPAT [53-56], 5-OH-DPAT being nearly as potent as 2. The 8-hydroxy isomer (8-OH-DPAT) has been shown to be a potent 5-hydroxytryptamine (5-HT) receptor agonist [52,56] with only minor dopaminergic properties [57]. The 6-hydroxy-5-methyl analogue 7 seems to be weakly dopaminergic [44]. The peripheral and central dopaminergic effects of the



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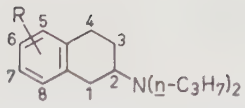

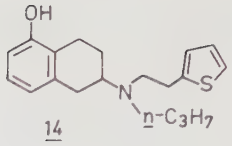

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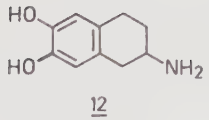
Compound	R
2	5,6-diOH
3	6,7-diOH
4	7,8-diOH
5	5,7-diOH
6	5,8-diOH
5-OH-DPAT	5-OH
6-OH-DPAT	6-OH
7-OH-DPAT	7-OH
8-OH-DPAT	8-OH
7	6-OH, 5-CH_3
8	5-OH, 6-CH_3
9	5-OH, 6-CH_2OH
10	5-OH, 6-CHO
11	H



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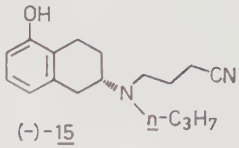
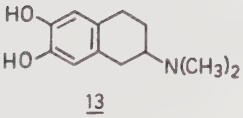


(-)-15



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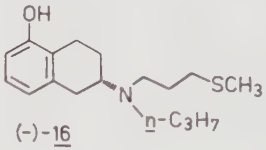


(-)-16

5-hydroxy-6-methyl derivative 8 [58] have been suggested to derive from metabolic activation to the dopaminergic 9 or 10 [59].

Also the nonhydroxylated 11 has been reported to induce dopaminergic effects [44,45,55,60].

In general, free phenolic function(s) gives higher potency than the corresponding methyl ether(s) [44,46]

2.3.2 Substitution at the nitrogen

In the 5,6-diOH series of 2-aminotetralins, the N,N-di-n-propyl homolog 2 is the most potent DA agonist. Shorter (H, CH_3, C_2H_5) or longer (n-C_4H_9) N-substituents give lower potency or complete loss of activity [44,45]. On the other hand, the N,N-di-n-propyl substituted 3 did not show increased dopaminergic potency in comparison with the corresponding primary amine 12 (ADTN) [61,62]. The N,N-dimethyl analogue 13 ("TL99") was first reported to be a

selective DA autoreceptor agonist [63]. However, recent studies have shown that it stimulates postjunctional DA receptors [64-65] and also α_2-adrenoceptors.

The effects of N-substitution have been studied extensively in a series of 2-amino-5-hydroxytetralins [46]. 2-Amino-5-hydroxytetralins bearing at least one N-n-propyl group had the highest potency. Recently, compound 14 [49,66-68] was described to be the most potent DA D_2-agonist encountered to date. In addition, (-)-15 and (-)-16 have pronounced dopaminergic effects [69].

2.3.3 Size of the nonaromatic ring

Several studies have shown that contraction [70-73] or expansion [70,73-75] of the nonaromatic ring in the 2-aminotetralin skeleton, give compounds with decreased dopaminergic activity.

2.3.4 Stereochemistry

The more potent enantiomers of the 5-hydroxy- and 5,6-dihydroxy-2-aminotetralin analogs have the 2S-configuration [53,76-83]. These enantiomers are homochiral with (R)-apomorphine. However, in the 7-hydroxy and 6,7-dihydroxy

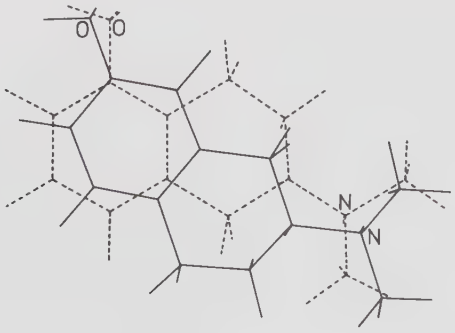


Figure 1. Computer generated fit of (2S)-5-OH-DPAT (dashed lines) and (2R)-7-OH-DPAT (solid lines). For clarity, only the dimethylamino moieties are shown.

derivatives, the dopaminergic activity resides in the 2*R*-enantiomers [76,82,83]. It has been proposed, by McDermed *et al.* [76,78,79], that the dopaminergic activity of (2*S*)-*2*, (2*S*)-5-OH-DPAT, (2*R*)-*12*, and (2*R*)-7-OH-DPAT can be rationalized by fitting the compounds as shown in Fig. 1.

3 SCOPE OF THE PRESENT INVESTIGATION

This investigation is part of a research project aimed at developing compounds with selectivity for central monoaminergic receptors.

The specific aim of the present study has been to investigate SAR for DA D2-receptor agonists.

By use of the potent DA D_2-receptor agonists 5-OH-DPAT and 7-OH-DPAT as basic structures, the effects of C1- and C3-methyl substitution in the nonaromatic ring (Papers I-VI) have been studied.

Conformational analysis by use of X-ray crystallography, ^{1}H- and ^{13}C NMR spectroscopy and molecular mechanics (MMP2) calculations have been made in an attempt to correlate pharmacological effects with the conformational preferences (Papers IV-VI).

The C1- and C3-methyl substituted 2-aminotetralins have been synthesized from the corresponding 1-methyl-2-tetralones and 3-methyl-2-tetralones, respectively. The synthesis of 5-, 7- and 8-methoxy-3-methyl-2-tetralones are presented in Papers VII and VIII.

4. PHARMACOLOGY

The compounds were tested *in vivo* by use of biochemical and behavioural methods in reserpinized and non-pretreated rats [85-88]. Some compounds were also tested for interactions with the DA receptor agonist 5,6-dihydroxy-2-(di-*n*-propylamino)tetralin (2) [44,46,47] *in vivo*. *In vitro* radioligand binding studies were performed with ^{3}H-spiroperidol [40,89] and ^{3}H-NPA [90] as ligands.

4.1 The biochemical assay

The concept of the *in vivo* biochemical assay is that a DA receptor agonist will stimulate the DA receptors and through regulatory feed-back systems induce a decline in tyrosine hydroxylase activity. Thus, a DA receptor agonist will reduce the synthesis rate of DA in the presynaptic neuron (for discussion of the experimental design and the underlying concepts, see e.g. refs. 85-88). The DOPA formation, determined after *in vivo* inhibition of the aromatic-L-amino acid decarboxylase by 3-hydroxybenzylhydrazine hydrochloride (NSD 1015), in the limbic, striatal and hemispheral brain parts is taken as an indirect measure of DA synthesis rate. DA receptor agonists decrease DOPA formation in reserpinized as well as in non-pretreated rats. Similarly, the 5-HTP formation in reserpinized and non-pretreated rats is expected to be decreased by 5-HT receptor agonists. The DOPA levels in reserpinized rats are not expected to be affected by a DA receptor antagonist. However, an antagonist will increase the DA synthesis rate in non-pretreated rats [91-93]. Central presynaptic DA receptors (autoreceptors) are considered to belong to the D_2 receptor category [94,95]. The ED_{50}-values for reducing the DOPA accumulation in DA-dominated brain regions of reserpinized rats are taken as measures of presynaptic DA receptor- and thus, D_2 receptor-stimulating abilities for the compounds under evaluation (cf. refs. 46,70).

Dose-response curves which were based on at least four dose levels, were constructed. The ED_{50}-value is the dose required to obtain 50% of the maximal DOPA or 5-HTP reduction (agonists) or DOPA enhancement (antagonists).

4.2 Behavioural observations

The behavioural observations and the locomotor activity recordings were carried out in motility meters as previously described [85-88].

Postsynaptic DA receptor agonists induce locomotor activity and stereotyped behaviour such as sniffing, rearing and licking in reserpinized rats [96,97]. In contrast, DA receptor antagonists or selective presynaptic DA receptor (DA autoreceptor) agonists are not expected to antagonize the reserpine induced akinesia. In non-pretreated rats, pre- and postsynaptic DA receptor agonists (such as (R)-apomorphine [21-23]) induce hypomotility after low doses and hypermotility with stereotypies after high doses. This has been suggested to reflect a stimulation of presynaptic DA receptors at low doses and a stimulation of postsynaptic DA receptors at high doses [98]. Classical DA receptor antagonists (such as haloperidol [92]) produce hypomotility and induce catalepsy at high doses [92]. This latter effect is probably related to antagonism of postsynaptic DA receptors. It has been reported that low doses of DA receptor antagonists such as haloperidol [99-101], spiperone [102], (-)-sulpiride [101], and pimozide [103] induce behavioural stimulation in non-pretreated rats. Most likely, these results reflect antagonism at presynaptic DA-receptors. In fact, low doses of the DA antagonist molindone [104], has been shown to antagonize presynaptic DA receptors selectively, thereby indirectly causing an activation of postsynaptic DA receptors.

In reserpinized rats, central 5-HT receptor agonists produce a syndrome characterized by flat body posture, forepaw

extension and treading, hindlimb abduction, tremor in the forebody and Straub tail reaction [105-106].

4.3 Interactions with 5,6-dihydroxy-2-(di-n-propylamino)-tetralin *in vivo*

A modification [107] of the recently described [108-111] *in vivo* binding assay for displacement of the potent DA receptor agonist 5,6-dihydroxy-2-(di-n-propylamino)tetralin (2) [44,46,47] from DA receptor binding sites in the rat striatum, has been used. In addition, antagonism of hyperlocomotion and hypothermia induced by 2 were studied.

4.4 *In vitro* binding

The binding to striatal DA D_2-receptors *in vitro* was evaluated in competition experiments with the DA antagonist ^{3}H-spiroperidol [40,89] and the DA agonist ^{3}H-NPA [90]. The pIC_{50} values obtained from the competition experiments under the conditions used for the ^{3}H-spiroperidol binding assay may be considered to be mainly related to binding to the D_{2low} affinity state. ^{3}H-NPA may be considered to mainly label the high affinity state of the D_2-receptor.

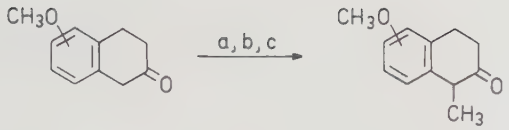
5 SYNTHESIS

All phenolic compounds described in Papers I-III and V-VI were prepared from the corresponding methoxy derivatives by demethylation in aqueous 48% hydrogen bromide. The phenolic amino hydrochlorides were obtained from the initially formed hydrobromides by halogen interchange (Papers II-III and V-VI).

5.1 Methyl substituted 2-tetralones

5.1.1 C1-Methyl substituted 5- and 7-methoxy-2-tetralones (Papers I-III, VI, and Scheme 1)

Scheme 1



17 5-OCH_3
18 7-OCH_3

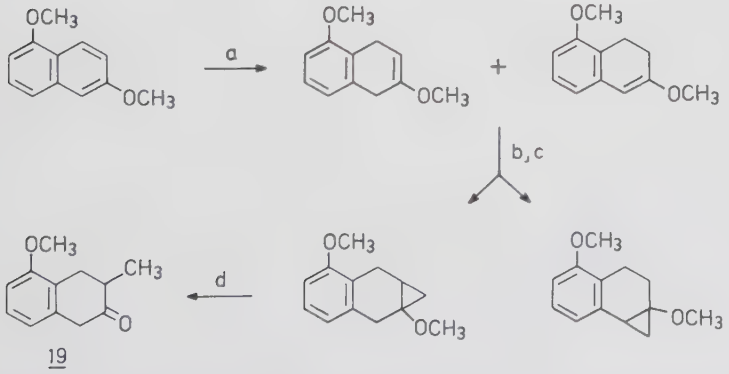
Reagents: a = Pyrrolidine, TsOH; b = CH_3I; c = H^+, H_2O

These 2-tetralones were prepared as depicted in Scheme 1. Methylation of the pyrrolidine enamines of the 2-tetralones, followed by hydrolysis, gave ketones 17 [112] and 18 [113].

5.1.2 C3-Methyl substituted 5-, 7-, and 8-methoxy-2-tetralones (Papers V-VIII and Schemes 2-4)

Three different synthetic routes were evaluated for the syntheses of the 3-methyl-2-tetralones:
(A) A regioselective sodium reduction of a 2-methoxy-naphthalene followed by cyclopropanation [114-116] of the resulting enol ethers and acid catalyzed ring opening [117-118] (Scheme 2).

Scheme 2



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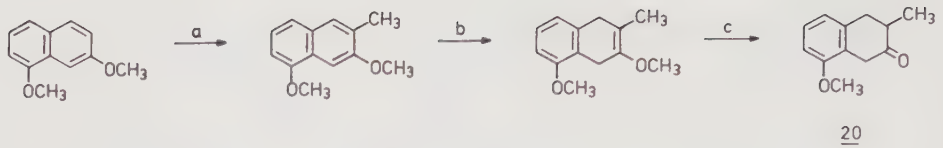
Reagents: a = Na, i-C_3H_7OH; b = $Zn(C_2H_5)_2$, CH_2I_2; c = flash chromatography; d = H^+, H_2O, MeOH

Scheme 3

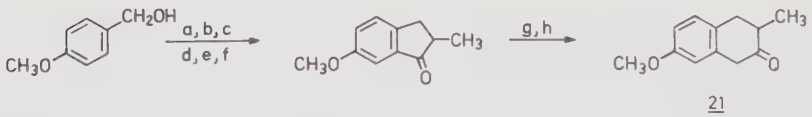


20

Reagents: a = n-BuLi, THF, CH_3I; b = Na, C_2H_5OH; c = H^+, H_2O, CH_3OH

(B) A regioselective methylation [119] of a 2-methoxynaphthalene followed by dissolved metal reduction and acid hydrolysis of the enol ether thus formed (Scheme 3). (C) thallium (III)-promoted ring expansion of a 2-methyl-1-indanone [120] (Scheme 4).

Scheme 4



21

Reagents: a = $SOCl_2$; b = $NaCCH_3(COOC_2H_5)_2$; c = KOH, H_2O; d = Δ;
e = $SOCl_2$; f = $AlCl_3$; g = $(Ph)_3P{=}CH_2$; h = $Tl(ONO_2)_3$, CH_3OH

The results obtained showed that route A was preferred for the synthesis of 19 (overall yield = 80% from 1,6-dihydroxynaphthalene), route B for the synthesis of 20 (overall yield = 77% from 1,7-dihydroxynaphthalene), and route C for the synthesis of 21 (overall yield = 37% from 4-methoxybenzyl alcohol).

5.2 C1- And C3-methyl substituted 5-hydroxy-2-(di-n-propylamino)tetralins (Papers I,V and Schemes 5-6)

trans-2-Amino-5-methoxy-1-methyltetralin (22) was prepared from the oxime of 17 by reduction with sodium in 2-propanol (Scheme 5). The reaction produced a mixture of trans and cis isomers [60% diastereomeric excess (% de); GC-analysis].

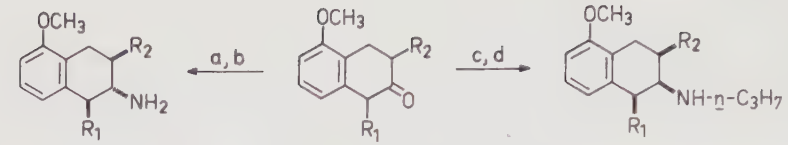
Pure trans was obtained by fractional crystallization of the hydrochlorides. To confirm the trans stereochemistry, compound 22 was also synthesized from 23 by a stereospecific hydroboration-amination sequence [121] (Scheme 6). The primary amine 22 was converted to the tertiary amine 25 by a N-acylation-reduction sequence via the secondary amine 24. trans-2-Amino-5-methoxy-3-methyltetralin (26) was prepared from 19 by use of the method used for the preparation of 22; 80% de (^{1}H NMR analysis) was obtained in the reduction of the oxime. Compound 26 was N-n-propylated by acylation followed by reduction, or N,N-di-n-propylated by alkylation with 1-iodopropane to afford 27 or 28, respectively.

cis-1-Methyl-2-(n-propylamino)tetralin (29) was obtained by reductive amination of 17 (Scheme 5); The catalytic hydrogenation of the intermediate imine afforded a mixture of cis and trans stereoisomers (92% de; GC-analysis). Pure 29 was obtained by fractional crystallization of the hydrochlorides. N-Acylation of 29 followed by reduction gave 30. cis-3-Methyl-2-(n-propylamino)tetralin 31 was synthesized from 19 by use of the reductive amination procedure described above for 29 (54% de; capillary-GC analysis). N-Alkylation of 31 with 1-iodopropane gave 32. 5-Methoxy-1,1-dimethyl-2-(di-n-propylamino)tetralin (33) was prepared from 5-methoxy-1,1-dimethyl-2-tetralone [122] via reductive amination, N-acylation and $LiAlH_4$ reduction.

5.2.1 Resolutions and absolute configurations (Papers II-V and Schemes 7-8)

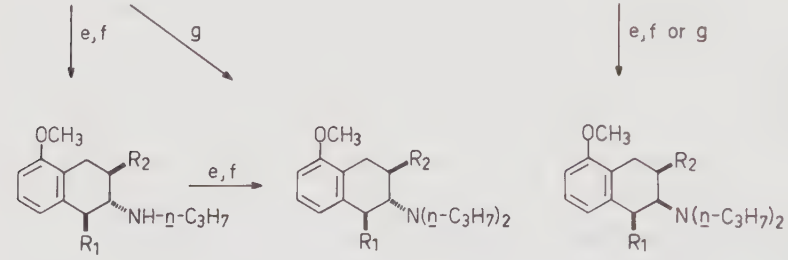
The racemic trans-amine 24 was converted to the diastereomeric (R)-O-methylmandelic amides (34 and 35), which were separated by use of flash chromatography (Scheme 7; compare refs. 123 and 124). The diastereomeric excess of 34 and 35 was determined by HPLC-analysis (see Table 1). The separated amides were treated with potassium-tert-butoxide in tetrahydrofuran [123,125] to afford a mixture of the secondary amine ((+)-24 or (-)-24) and the corresponding N-formyl derivative [123,82]. The latter were converted to

Scheme 5



22 $R_1 = CH_3$; $R_2 = H$ 17 $R_1 = CH_3$; $R_2 = H$ 29 $R_1 = CH_3$; $R_2 = H$

26 $R_1 = H$; $R_2 = CH_3$ 19 $R_1 = H$; $R_2 = CH_3$ 31 $R_1 = H$; $R_2 = CH_3$

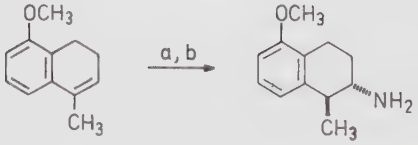


24 $R_1 = CH_3$; $R_2 = H$ 25 $R_1 = CH_3$; $R_2 = H$ 30 $R_1 = CH_3$; $R_2 = H$

27 $R_1 = H$; $R_2 = CH_3$ 28 $R_1 = H$; $R_2 = CH_3$ 32 $R_1 = H$; $R_2 = CH_3$

Reagents: a = $NH_2OH \cdot HCl$, NaOAc; b = Na, i- C_3H_7OH; c = n-$C_3H_7NH_2$, TsOH; d = H_2, Pd(C); e = C_2H_5COCl, $(C_2H_5)_3N$; f = $LiAlH_4$; g = n-C_3H_7I, K_2CO_3

Scheme 6



23 22

Reagents: a = $NaBH_4$, $BF_3 \cdot (C_2H_5)_2O$; b = NH_2OSO_3H

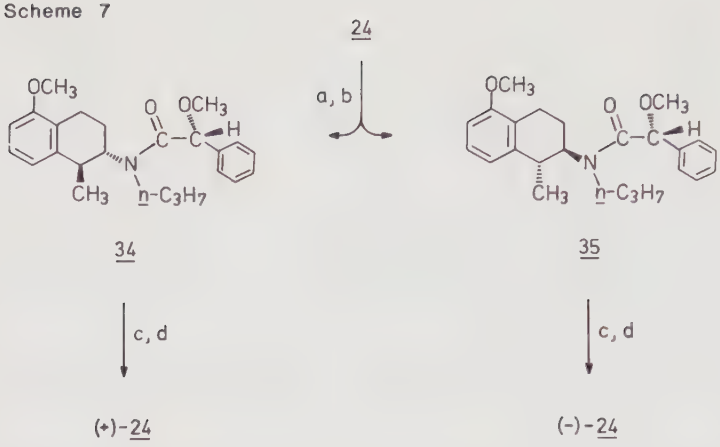
(+)-24 or (-)-24 by treatment with methyllithium in ether. The tertiary amines (-)-25 and (+)-25 were prepared from (+)-24 and (-)-24, respectively, by N-acylation followed by reduction of the resulting amides (see Scheme 5).

The trans amine 27 was resolved into the (+)- and (-)-enantiomers by fractional crystallization of the diastereomeric dibenzoyltartrates. The per cent enantiomeric excess (Table 1) was estimated by capillary-GC analysis of the (R)-O-methylmandelic amides of (+)-27 and (-)-27. N-Alkylation of (+)-27 and (-)-27 with 1-iodopropane gave (+)-28 and (-)-28, respectively.

The racemic tetralone 17 was converted to (-)-36 and (+)-36 via the enantiomeric amines (-)- and (+)-37, respectively, according to a slightly modified literatur procedure [126-128] (see Scheme 8). Initially, the reductive amination seemed to proceed under a remarkable stereochemical control. However, when the conversion of 17 to (+)-37 was repeated with a new batch of Pd(C), a mixture of (+)-37 and 38 was formed (80% de as indicated by ^{1}H and ^{13}C NMR spectroscopy; see Scheme 9). The separation of the diastereomeric amines (+)-37 and 38 was accomplished by column chromatography of the corresponding trifluoroacetamides 39 and 40. The diastereomeric excess of the separated trifluoroacetamide 40 was determined by capillary-GC to be 96%. The trifluoroacetamide function was cleaved by use of sodium borohydride [129]. Hydrogenolysis of the benzylic C-N bond of (-)- and (+)-37 gave (-)- and (+)-36, respectively. In order to confirm the enantiomeric excess, (-)-36 and (+)-36 were converted to the corresponding (R)-O-methylmandelic amides and analyzed by ^{1}H NMR spectroscopy (see Table 1). Alternatively, racemic 29 was resolved by chromatographic separation of the corresponding diastereomeric (R)-O-methylmandelic amides in analogy with the resolution of 24.

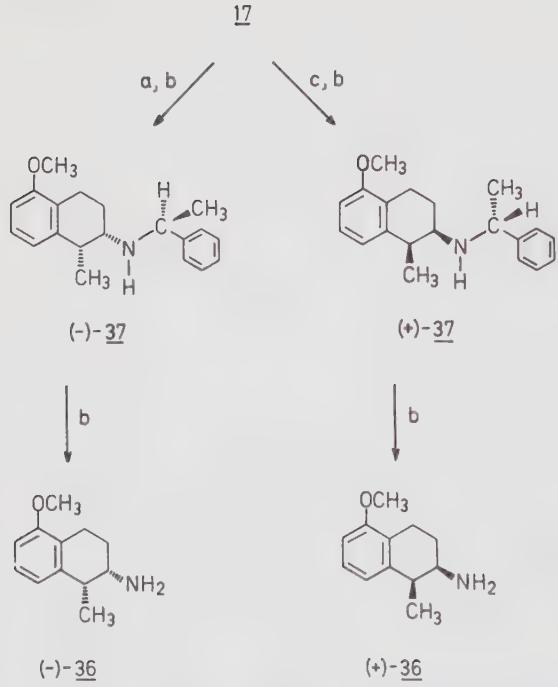
Compound 31 was resolved into the (+)- and (-)-enantiomers by fractional crystallization of the diastereomeric di-p-toluoyltartrates. The enantiomeric excess of (+)-31 and

Scheme 7



Reagents: a=(R)-2-Methoxy-2-phenylacetyl chloride; b = separation of the diastereomeric amides; c=t-C_4H_9OK; d=CH_3Li

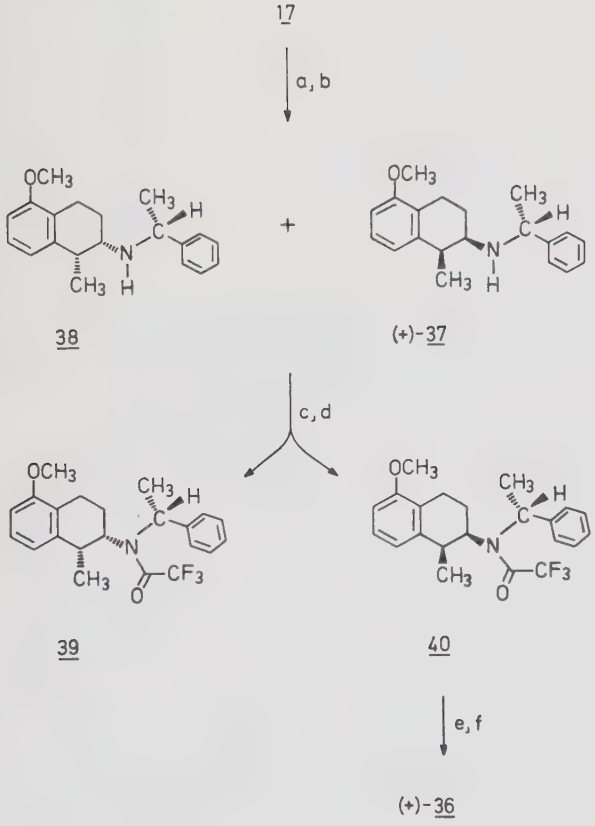
Scheme 8



Reagents: a= (S)-(-)-1-Phenylethylamine; b=H_2, Pd(C); c=(R)-(+)-1-phenylethylamine

(-)-31 were determined by capillary-GC analyses of the corresponding (R)-O-methylmandelic amides (see Table 1). N-Alkylation of (+)-31 and (-)-31 as depicted in Scheme 5 gave (+)-32 and (-)-32, respectively.

Scheme 9

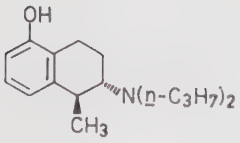


Reagents: a = (R)-(+)-1-Phenylethylamine; b = H_2, Pd(C); c = $(CF_3CO)_2O$, $(C_2H_5)_3N$; d = separation of the diastereomeric amides; e = $NaBH_4$; f = H_2, Pd(C)

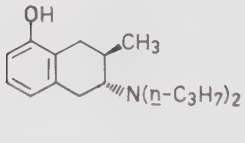
Table 1 Resolution of Some 2-Aminotetralins

Compd	Method[a]	Yield %	Anal. method for determ. of %ee[b]	%ee
(+)-24	A	39	HPLC	98
(-)-24	A	37	HPLC	96
(+)-27	B	46	capillary-GC	94
(-)-27	B	38	capillary-GC	94
(+)-31	C	72	HPCL	96
(-)-31	C	68	HPCL	96
(+)-36	D	23	^{1}H NMR	>90
(-)-36	D	19	^{1}H NMR	>90
(+)-50	B	62	capillary-GC	92
(-)-50	B	60	capillary-GC	100
(+)-53	C	43	HPLC	96
(-)-53	C	56	HPLC	96

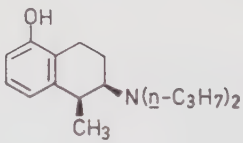
a) A= separation of diastereomeric (R)-O-methylmandelic amides, followed by cleavage of the amide function, B= fractional crystallization of diastereomeric dibenzoyltartrates, C= fractional crystallization of diastereomeric di-p-toluoyltartrates, D= asymmetric synthesis, b) the enantiomeric excess (%ee) was determined indirectly via the diastereomeric excess of the corresponding (R)-O-methylmandelic amide.



(-)-41



(-)-42



(+)-43

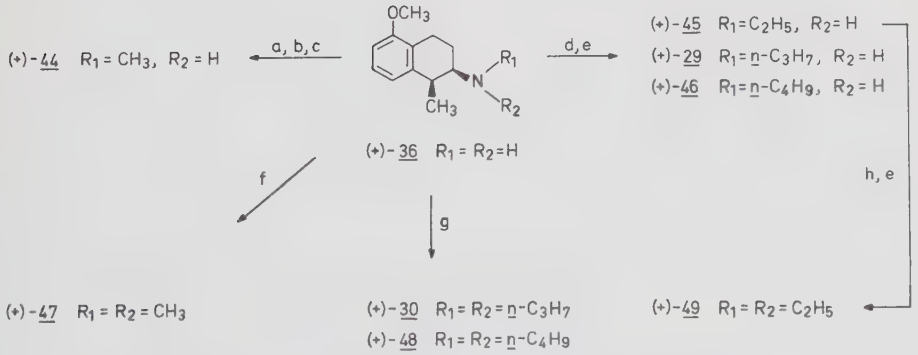
X-Ray crystallography established the absolute configurations to be 1S,2S of (-)-41·HCl, 2R,3R of (-)-42·HBr [130], 1S,2R of (+)-43·HBr and 2R,3S of (-)-32·HCl. This also established the absolute configuration of the other resolved analogs of these compounds.

5.2.2 N-Alkylated derivatives of resolved cis-2-amino-5-methoxy-1-methyltetralin (Paper III and Scheme 10)

N-Alkyl derivatives of (+)-36 were prepared as outlined in Scheme 10; the N-methyl derivative (+)-44 was prepared by methylation of the trifluoroacetamide of (+)-36, followed by hydrolysis of the amide [131]. The secondary amines, (+)-45, (+)-29, and (+)-46 were prepared by acylation of (+)-36 with the appropriate acyl chloride, followed by reduction of the crude amides. Reductive methylation of (+)-36 with formaldehyde and sodium cyanoborohydride [51] gave (+)-47. The N,N-dialkyl derivatives (+)-30 and (+)-48 were prepared by alkylation of (+)-36 with 1-iodopropane and 1-bromobutane, respectively. Acylation of (+)-45 with acetyl chloride, followed by reduction of the resulting amide gave (+)-49.

The N-alkylated derivatives of (-)-36 [(-)-47, (-)-30, (-)-48 and (-)-49] were prepared from (-)-36 in the same manner.

Scheme 10

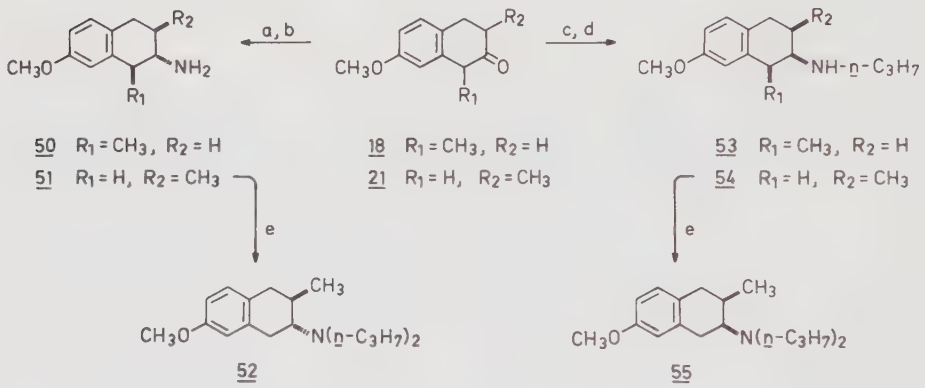


Reagents: a = $(CF_3CO)_2O$, $(C_2H_5)_3N$; b = KH, CH_3I; c = KOH, H_2O, CH_3OH; d = RCOCl, $(C_2H_5)_3N$; e = $LiAlH_4$; f = HCHO, $NaCNBH_3$; g = R-X, K_2CO_3; h = CH_3COCl, $(C_2H_5)_3N$

3 C1- And C3-methyl substituted 7-hydroxy-2-(di-n-propylamino)tetralins (Paper VI and Scheme 11)

trans-2-Amino-7-methoxy-1-methyltetralin 50 and trans-2-amino-7-methoxy-3-methyltetralin 51 were obtained from 18 and 21, respectively, by the oxime reduction procedure as previously described in Section 5.1 (Scheme 11). The diastereomeric excess in the reduction of the oximes to 50 and 51 was 46% (GC analysis) and 60% (^{1}H NMR analysis), respectively. N-Alkylation of 51 with 1-iodopropane gave 52.

Scheme 11

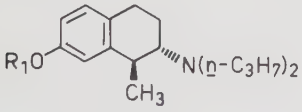


Reagents: a = $NH_2OH \cdot HCl$, NaOAc; b = Na, i-C_3H_7OH; c = n-$C_3H_7NH_2$, TsOH; d = H_2, Pd(C); e = n-C_3H_7I, K_2CO_3

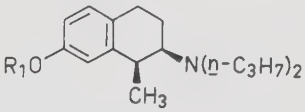
cis-7-Methoxy-1-methyl-2-(n-propylamino)tetralin (53) and cis-7-methoxy-3-methyl-2-(n-propylamino)tetralin (54) were prepared from 18 and 21, respectively, by reductive amination (Scheme 11). The diastereomeric excess in the reductive amination to 53 and 54 was 60% (GC-analysis) and 64% (capillary-GC analysis), respectively. N-alkylation of 54 with 1-iodopropane gave 55.

5.3.1 Resolutions and absolute configurations

Racemic 50 and 53 were resolved into the (+)- and (-)-enantiomers by fractional crystallization of the diastereomeric dibenzoyltartrates and di-p-toluoyltartrates, respectively. The enantiomeric excess of (+)-50, (-)-50, (+)-53 and (-)-53 was determined by capillary-GC [(+)-50 and (-)-50] and HPLC [(+)-53 and (-)-53] analyses of the corresponding (R)-O-methylmandelic amides (see Table 1). N-Alkylation of (+)-50, (-)-50, (+)-53 and (-)-53 with 1-iodopropane gave (-)-56, (+)-56, (+)-57 and (-)-57, respectively. The absolute configuration of (+)-58·HCl and (+)-59·HCl was established by X-ray crystallography to be (1S,2S) and (1S,2R), respectively. This also establishes the absolute configuration of the resolved derivatives of (+)-58 and (+)-59.



(+)-56 $R_1 = CH_3$
(+)-58 $R_1 = H$



(+)-57 $R_1 = CH_3$
(+)-59 $R_1 = H$

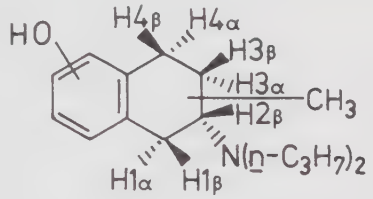
6 CONFORMATIONAL ANALYSIS

A combination of ^1H and ^{13}C NMR spectroscopy, X-ray crystallography and molecular mechanics (MMP2) calculations was used to determine the three-dimensional structures and conformational preferences of a number of compounds.

6.1 ^1H And ^{13}C NMR spectroscopy (Papers IV-VI)

Use of 400-MHz spectroscopy (JEOL GX-400 spectrometer; 0.1 M CD_3OD solutions) allowed analysis of most of the resonances by first order approximations, and COSY spectroscopy allowed assignments of nearly all proton resonances. The coupling constants were refined by spin-spin simulation using a JEOL FASNO 5 NMR spectrum simulation program. Observed vicinal

Table 2 Coupling Constants in ^1H NMR Spectra of Some 2-Aminotetralins in CD_3OD



Compd	OH-pos.	CH_3-pos.	coupling constants (J, Hz)										
			$J_{1\alpha,1\beta}$	$J_{1\alpha,2\beta}$	$J_{1\beta,2\beta}$	$J_{2\beta,3\alpha}$	$J_{2\beta,3\beta}$	$J_{3\alpha,3\beta}$	$J_{3\alpha,4\beta}$	$J_{3\alpha,4\alpha}$	$J_{3\beta,4\beta}$	$J_{3\beta,4\alpha}$	$J_{4\alpha,4\beta}$
5-OH-DPAT·HCl	5		a	9.3	4.5	10.5	2.5	-10.5	10.5	5.6	5.8	3.0	-16.0
41·HCl	5	1β		3.5		7.2	4.3	-14.2	5.7	7.6	7.5	5.5	-17.3
43·HCl	5	1α			4.4	12.7	2.9	-12.2	12.0	6.5	7.1	1.5	-18.0
42·HCl	5	3β	-15.8	9.0	5.4	≈8.0[b]			9.3	5.0			-16.8
60·HCl	5	3α	-15.8	12.0	5.6		2.7				4.9	1.7	-16.8
61·HCl	5	1α,1β				10.6	2.6	-13.0	10.9	5.5	6.0	3.8	-17.4
7-OH-DPAT·HCl	7		-15.6	11.2	5.6	11.6	3.0	-12.0	11.8	5.8	5.0	2.9	-16.5
58·HCl	7	1β		3.6		a	5.5	-13.8	a	a	5.6	5.5	a
59·HCl	7	1α			4.4	12.4	3.2	-12.2	11.8	6.5	6.4	2.0	-17.4
62·HCl	7	3β	-15.6	9.2	6.0	≈8.0[b]			9.1	5.1			-15.7
63·HCl	7	3α	-15.9	11.8	5.8		2.8				5.0	a	-17.0

a) Not determined, b) Estimated from spin-spin simulations.

coupling constants, presented in Table 2, indicate that 5-OH-DPAT·HCl, 43·HCl, 42·HCl, 60·HCl, 61·HCl, 7-OH-DPAT·HCl, 59·HCl, 62·HCl and 63·HCl preferentially assume half-chair conformations with pseudoequatorial dipropylammonium substituents in methanol-d_4; the large dipseudoaxial coupling constants $J_{1\alpha,2\beta}$ in 5-OH-DPAT·HCl, 42·HCl, 60·HCl, 7-OH-DPAT·HCl, 62·HCl, and 63·HCl and $J_{2\beta,3\alpha}$ in 5-OH-DPAT·HCl, 43·HCl, 42·HCl, 61·HCl, 7-OH-DPAT·HCl, 59·HCl, and 62·HCl establish the C2-hydrogens as pseudoaxial and, thus, the dipropylammonium groups as pseudoequatorial [132-134]. In addition, the large value of $J_{3\alpha,4\beta}$ in 5-OH-DPAT·HCl, 43·HCl, 42·HCl, 61·HCl, 7-OH-DPAT·HCl, 59·HCl, and 62·HCl and the small value of $J_{3\beta,4\alpha}$ in 5-OH-DPAT·HCl, 43·HCl, 60·HCl, 61·HCl, 7-OH-DPAT·HCl, and 59·HCl provide further support for the suggested half-chair conformations.

No large vicinal coupling constants were present in spectra of 41·HCl and 58·HCl. Also the spectrum of 2-amino-6,7-dihydroxy-2-methyltetralin (in $CDCl_3$) has been observed to lack large vicinal (dipseudoaxial) coupling constants [133]. These spectra may reflect a time average of equilibrating tetralin ring conformations in solution.

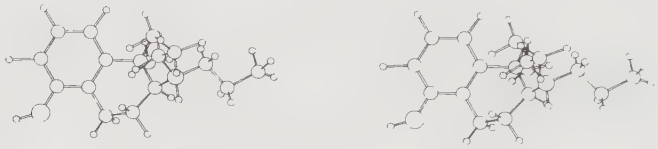
^{13}C NMR spectroscopy (JEOL FX-90Q spectrometer; 0.1 M CD_3OD solutions) revealed that rotation around the C2-N bond is slow on the NMR time scale in the hydrochlorides of 41-43 and 58-63. This was evident from the magnetic nonequivalence of Cα and Cα' (41·HCl, 42·HCl, 60·HCl, 61·HCl, 58·HCl, 62·HCl, and 63·HCl) and of Cβ and Cβ' (43·HCl, 61·HCl, 59·HCl, and 62·HCl) (for definition of Cα, Cα', Cβ, and Cβ' see ref. 134].

6.2 X-Ray crystallography (Papers IV-VI)

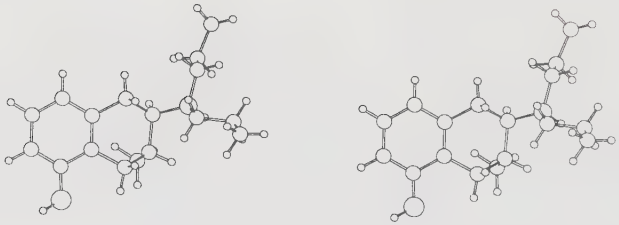
Figure 2 shows stereoscopic representations of the solid state conformations of (-)-(1S,2S)-41·HCl, (-)-(2R,3R)-42·HBr, (+)-(1S,2S)-58·HCl, (+)-(1S,2R)-59·HCl, and of the A and B molecules of (+)-(1S,2R)-43·HBr and (-)-(2R,3S)-32·HCl. The solid state conformations of (+)-43·HBr and

(-)-32·HCl were similar to low energy conformations identified in the molecular mechanics (MMP2) calculations, whereas the solid state conformations of (-)-41·HCl, (-)-42·HBr, (+)-58·HCl, and (+)-59·HCl correspond to MMP2 conformations with energies 3.3, 3.7, 4.2, and 3.2 kcal/mol above the respective global minimum.

a

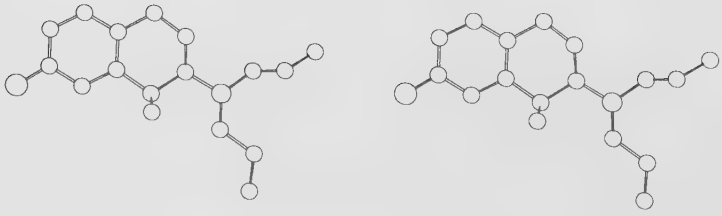


b



c

d



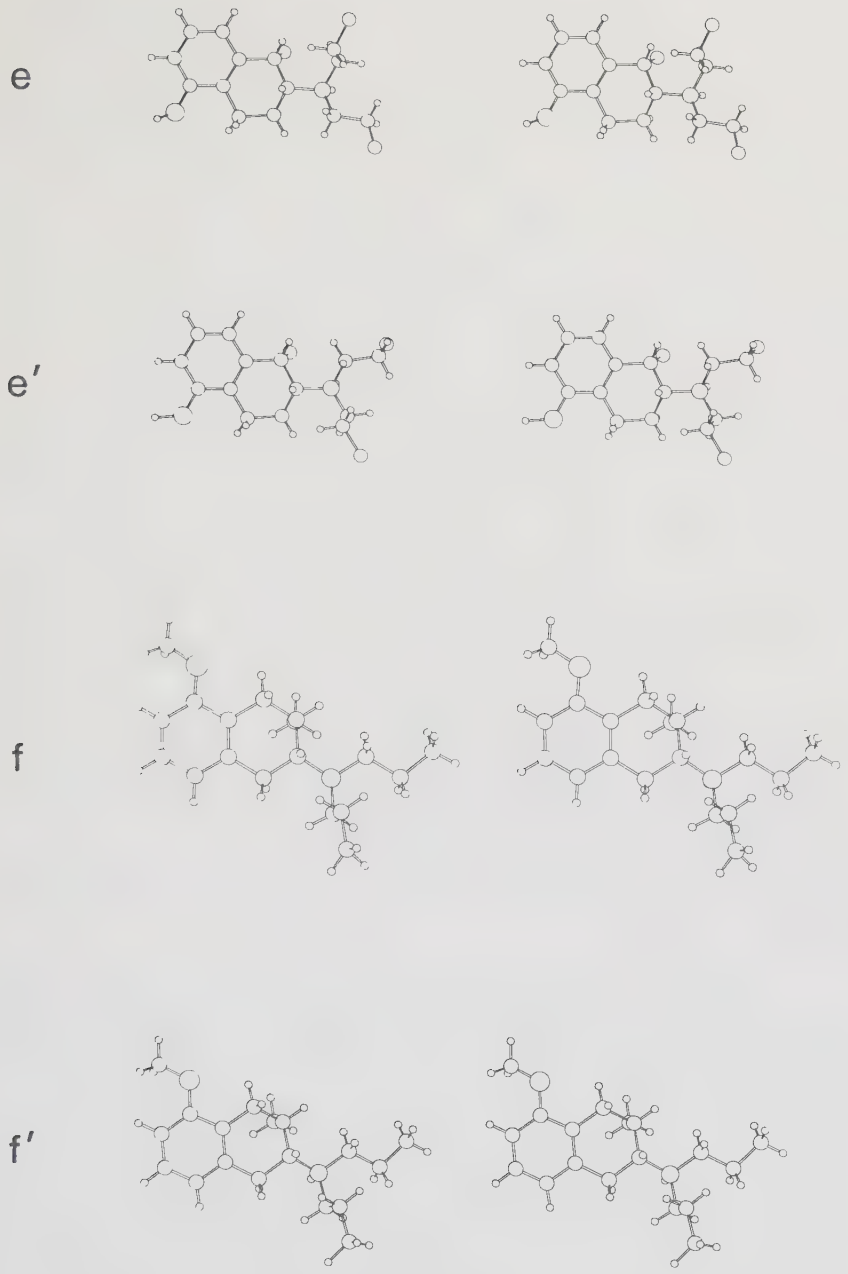


Figure 2. Stereoscopic representations of the solid state conformation of (-)-(1S,2S)-41·HCl (a), (-)-(2R,3R)-42·HBr (b), (+)-(1S,2R)-58·HCl (c), (+)-(1S,2R)-59·HCl (d), and the A and B molecules of (+)-(1S,2R)-43·HBr (e,e') and (-)-(2R,3S)-32·HCl (f,f').

6.3 Molecular mechanics (MMP2) calculations (Papers IV-VI)

To identify conformations of (2S)-5-OH-DPAT, (1S,2S)-41, (1R,2S)-43, (2R,3R)-42, (2R,3S)-60, (2S)-61, (2R)-7-OH-DPAT, (1R,2R)-58, (1S,2R)-59, (2S,3S)-62, and (2S,3R)-63 with energies less than 2.5 kcal/mol above the respective global minimum, we applied a strategy which has been described in detail elsewhere [134]. For the calculations we utilized the MMP2 program developed by Allinger, modified as previously described [134]. Throughout, full energy minimization with respect to all internal coordinates was performed. All calculations were performed on the free bases. In the 5-hydroxy series, the starting geometry of the hydroxyl group was always set at τ(C4a,C5,O,H)=180° (test calculations have shown that conformations with τ(C4a,C5,O,H) around 0°, consistently have energies 0.2-0.4 kcal/mol above those of the corresponding conformations with τ(C4a,C5,O,H) around 180°). In the 7-hydroxy series, the starting geometry of the hydroxyl group was set at τ(C6,C7,O,H)=0° (test calculations have shown that conformations with τ(C6,C7,O,H) around 180°, consistently have energies equal those of the corresponding conformations with τ(C6,C7,O,H) around 0°). The structural modelling was performed by use of the interactive computer graphics program MIMIC (methods for interactive modelling in chemistry) [135].

To characterize the different conformations, two conformational parameters, the tetralin inversion angle Φ and the dihedral angle τ(C1, C2, N, N-H or electron pair) (τ_N), are of particular utility. The tetralin inversion angle Φ defines the conformation of the non-aromatic ring of any tetralin derivative (see Fig. 3). Φ is configurationally dependent, and enantiomeric conformations differ in Φ-values with ±180° [134]. In e.g. (2S)-2-aminotetralin a half-chair conformation with a pseudoequatorial amino group corresponds to Φ=0° while a half-chair conformation with a pseudoaxially oriented amino group corresponds to Φ=180° [134], and in (2R)-2-aminotetralin Φ=180° and Φ=0° correspond to half-chair conformations with a pseudoequatorial and pseudoaxial

amino group [136], respectively. The dihedral angle τ_N defines the relative direction of the N-H bond (or the electron pair) and indirectly, the preferred arrangement around the C(2)-N bond [77,134-136].

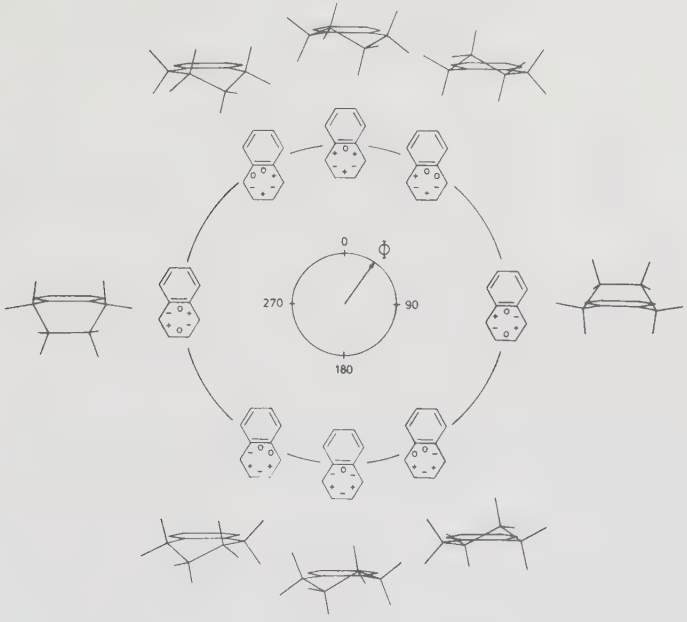
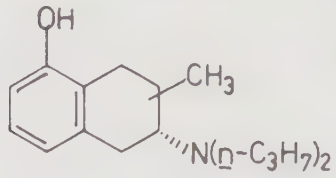


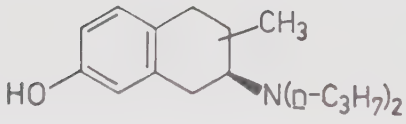
Figure 3. Tetralin inversion wheel which defines the relationship between tetralin ring conformation and the tetralin inversion angle Φ.

In general, the identified low energy conformations have Φ-values around 0° or 180°, that is, boat conformations do not appear to be energetically favourable in any of the compounds investigated. Based on the steric energies of the various conformations, Boltzmann distributions were estimated (see Table 3). All compounds except (2S)-5-OH-DPAT and (2R)-7-OH-DPAT, prefer to assume only one of the three possible dipropylamino group rotamers in tetralin conformations with Φ-values around 0° or 180°.

Table 3 Conformational Distribution of Some 2-Aminotetralins



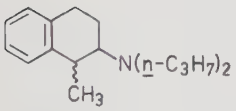
Compd	CH_3-pos.	$\phi \approx 0^\circ$			$\phi \approx 180^\circ$		
		$\tau_N \approx 60^\circ$	$\tau_N \approx 180^\circ$	$\tau_N \approx -60^\circ$	$\tau_N \approx 60^\circ$	$\tau_N \approx 180^\circ$	$\tau_N \approx -60^\circ$
(2S)-5-OH-DPAT		18 %	44 %	20 %	18 %	-	-
(1S,2S)-41	C1-trans	0.4 %	-	78 %	21 %	-	0.3 %
(1R,2S)-43	C1-cis	100 %	-	-	-	-	-
(2R,3R)-42	C3-trans	-	100 %	-	-	-	-
(2R,3S)-60	C3-cis	100 %	-	-	-	-	-
(2S)-61	C1,C1	-	-	58 %	-	-	42 %



Compd	CH_3-pos.	$\phi \approx 0^\circ$			$\phi \approx 180^\circ$		
		$\tau_N \approx 60^\circ$	$\tau_N \approx 180^\circ$	$\tau_N \approx -60^\circ$	$\tau_N \approx 60^\circ$	$\tau_N \approx 180^\circ$	$\tau_N \approx -60^\circ$
(2R)-7-OH-DPAT		-	-	17 %	19 %	46 %	18 %
(1R,2R)-58	C1-trans	0.4 %	-	20 %	79 %	-	0.4 %
(1S,2R)-59	C1-cis	-	-	-	-	-	100 %
(2S,3S)-62	C3-trans	-	-	-	-	100 %	-
(2S,3R)-63	C3-cis	-	-	-	-	-	100 %

7 STRUCTURE-ACTIVITY RELATIONSHIPS

Compounds 64 [44], 65 [133], and 66 [137,138] are 2-aminotetralins which are methyl substituted in the non-aromatic ring and have been tested for dopaminergic activity. Compound 64 showed moderate potency in eliciting stereotyped behavior, 65 was inactive as a DA_1 agonist and 66 was inactive at central DA receptors.



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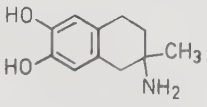

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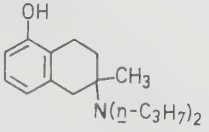
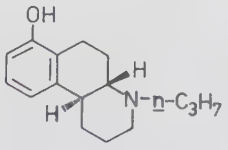


66

7.1 C5-Oxygenated 2-aminotetralins (Papers I-V)

The *in vivo* pharmacological results from some compounds are shown in Tables 4 and 5. Compound 61 appeared to be inactive *in vivo*. The C1-methyl substituted *trans* and *cis* isomers 41 and 43 seem to be equipotent as DA receptor agonists. Compound 41 was shown to have agonistic activity at both pre- and postsynaptic DA receptors while 43 appeared to lack prominent postsynaptic agonistic effects. The selectivity of 43 for presynaptic receptors and the low potency of 41 in comparison with the structurally related (±)-7-OHBQ [139] provided impetus for the resolution of these compounds. Thus, 41 and 43 were resolved into the enantiomers and, in addition, a number of derivatives were prepared.

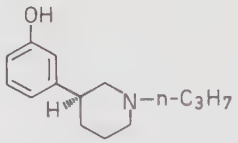


(4aS,10bS)-7-OHBQ

The active analogs of 41 and 43 were classified pharmacologically into four groups mainly based on the results from the biochemical and motor activity assays (see Tables 4 and 5);

(a) Classical pre- and postsynaptic DA receptor agonists [(1S,2S)-41, (1R,2S)-30 [88,140], (1R,2S)-43 [88,140]; Table 4]. Compound (1R,2S)-43 (ED_{50}≈320 nmol/kg) is more potent than (1S,2S)-41 and (1R,2S)-30. However, it is around hundredfold less potent than (S)-5-OH-DPAT (ED_{50}≈4 nmol/kg) [82]. It should be noted that the pharmacological classification of (1R,2S)-30 and (1S,2S)-41 is tentative. In agreement with earlier findings with C5-oxygenated 2-amino-tetralins; dipropylamino substituents and a free phenolic function give the most potent DA receptor agonists [46].

(b) DA receptor agonists with preferential action at presynaptic receptors [(1R,2S)-67, (1R,2S)-68; Tables 4 and 5]. These compounds appeared to have a profile similar to (S)-3-PPP [141,142], that is, they are agonists at presynaptic DA receptors and antagonists at postsynaptic DA receptors (mixed agonists-antagonists).

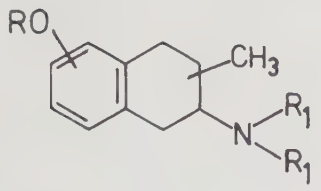


(S)-3-PPP

(c) Pre- and postsynaptic DA receptor antagonists [(1S,2R)-47, (1S,2R)-49 [143]; Table 5]. The in vivo pharmacological profile of these compounds are similar to that of classical neuroleptics such as haloperidol [92]. However, (1S,2R)-49 did not induce catalepsy at the doses tested.

(d) DA receptor antagonists with preferential action at presynaptic receptors [(1S,2R)-29, (1S,2R)-30, (1S,2R)-69, (1S,2R)-43 [88,140,143-146]; Table 5]. These compounds appear to represent a new class of compounds.

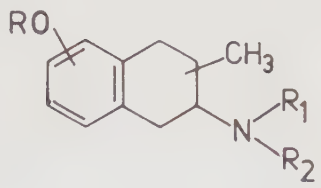
Table 4 Biochemical and Behavioural Effects in Reserpinized Rats



Compd	RO-	CH_3-pos.	R_1	ED_{50}[a] (μmol/kg s.c.) limbic	striatum	Motor Activity[b] Acc. counts/30 min
41	5-OH	C1-trans	n-Pr	0.66	0.73	406[c]
(1S,2S)-41	5-OH	C1-trans	n-Pr	7.3	7.9	19
(1R,2R)-41	5-OH	C1-trans	n-Pr	I[d]	I	NT[e]
43	5-OH	C1-cis	n-Pr	0.67	0.80	52[c]
(1R,2S)-30	5-OMe	C1-cis	n-Pr	5.5	5.8	8
(1R,2S)-43	5-OH	C1-cis	n-Pr	0.30	0.34	121***
(1R,2S)-67	5-OH	C1-cis	Me	28.0	25.0	7
(1R,2S)-68	5-OH	C1-cis	Et	1.4	1.6	5
61	5-OH	C1,C1	n-Pr	I	I	NT
(2R,3R)-42	5-OH	C3-trans	n-Pr	3.5	3.1	53***
(2S,3S)-42	5-OH	C3-trans	n-Pr	25.0	25.0	55***
(2R,3S)-60	5-OH	C3-cis	n-Pr	0.005	0.005	110***
(2S,3R)-60	5-OH	C3-cis	n-Pr	I	I	12
(2S)-5-OH-DPAT	5-OH	-	n-Pr	0.004[f]	0.004[f]	155*[f]
(2R)-5-OH-DPAT	5-OH	-	n-Pr	0.41[f]	0.65[f]	43*[f]
(1R,2R)-58	7-OH	C1-trans	n-Pr	I	I	8
(1S,2S)-58	7-OH	C1-trans	n-Pr	I	I	17*
(1S,2R)-59	7-OH	C1-cis	n-Pr	0.07[g]	0.06	50***
(1R,2S)-59	7-OH	C1-cis	n-Pr	3.5	3.0	20
62	7-OH	C3-trans	n-Pr	I	I	35*
63	7-OH	C3-cis	n-Pr	I	I	331***
(2R)-7-OH-DPAT	7-OH	-	n-Pr	0.01[f,h]	0.01[f]	46*[f]
(2S)-7-OH-DPAT	7-OH	-	n-Pr	1.9[f,i]	2.4[f]	33*[f]
(R)-Apomorphine				0.041[j]	0.044[j]	366***

a) Estimated dose giving a half-maximal decrease of the DOPA level in the rat brain, b) Motor activity for control, 3±1, statistics: *** $p<0.001$, * $p>0.05$ vs control, c) Acc. counts/60 min., d) Inactive, e) Not tested, f) From ref. 82, g) A 30% decrease in limbic and striatal 5-HTP formation was noted at 4.0 μmol/kg s.c., h) A 50% decrease in limbic and striatal 5-HTP formation was noted at 18 μmol/kg s.c., i) A 40% decrease in limbic and striatal 5-HTP formation was noted at 9.8 μmol/kg s.c.,j) From ref. 70.

Table 5 Biochemical and Behavioural Effects in Non-Pretreated Rats



Compd	RO-	CH_3- pos.	R_1	R_2	ED_{50}[a] (µmol/kg s.c.) limbic	ED_{50}[a] (µmol/kg s.c.) striatum	Motor Activity[b] per cent of controls
(1R,2S)-67	5-OH	C1-cis	Me	Me	8.5 (200 %)	8.5 (200 %)	15***
(1R,2S)-68	5-OH	C1-cis	Et	Et	c	c	40***
(1S,2R)-47	5-OMe	C1-cis	Me	Me	2.2 (330 %)	2.9 (410 %)	9***d
(1S,2R)-49	5-OMe	C1-cis	Et	Et	5.5 (300 %)	2.9 (410 %)	46*
(1S,2R)-29	5-OMe	C1-cis	n-Pr	H	4.6 (240 %)	4.4 (320 %)	159*(*)
(1S,2R)-30	5-OMe	C1-cis	n-Pr	n-Pr	12.8 (285 %)	9.6 (380 %)	70**
(1S,2R)-69	5-OH	C1-cis	n-Pr	H	9.0 (200 %)	16.0 (280 %)	125
(1S,2R)-43	5-OH	C1-cis	n-Pr	n-Pr	10.0 (240 %)	9.4 (340 %)	102
63	7-OH	C3-cis	n-Pr	n-Pr	11.0 (160 %)	7.5 (230 %)	119[e]
Haloperidol					0.19 (210 %)[f]	0.19 (310 %)[f]	3***d,g

a) Estimated dose giving a half-maximal decrease of the DOPA level in the rat brain, b) The dose tested was 52 µmol/kg s.c.; Motor activity for controls 232±14, statistics ***$p<0.001$, *(*)$p<0.025$, *$p<0.01$ vs control, c) A 40-50 % increase in the DOPA formation after 52 µmol/kg, d) Catalepsy was produced, e) The dose tested was 25 µmol/kg s.c., f) From ref. 92, g) The dose tested was 2.7 µmol/kg i.p.

Table 6 Affinities for Striatal ^{3}H-Spiroperidol and ^{3}H-NPA-binding Sites in vitro

Compd	^{3}H-Spiroperidol pIC_{50}	^{3}H-NPA pIC_{50}
(1S,2S)-41	<4	5.79
(1R,2R)-41	<4	4.28
(1R,2S)-43	5.42	7.53
(1S,2R)-43	5.15	6.56
61	<4	6.11
(2S)-5-OH-DPAT	6.24	8.24
(2R)-5-OH-DPAT	4.15	6.80

The above results indicate that both (2R)- and (2S)-enantiomers of C5-oxygenated 2-amino-1-methyltetralins may be able to bind to DA receptors and that only the (2S)-antipodes are able to activate the receptors. In general, a decrease in the size of the N-alkyl group(s) in the C5-oxygenated (1R,2S)-2-amino-1-methyltetralins, from n-propyl to ethyl or methyl, appears to increase the selectivity for activation of presynaptic receptors. In contrast, smaller N-substituent(s) in the enantiomeric (1S,2R)-series seem to increase the affinity to postsynaptic DA receptors. O-Methylation tends to increase DA receptor antagonistic activity [compare for example: (1S,2R)-69 and (1S,2R)-29; Table 5], whereas O-methylation in phenolic DA receptor agonists considerably decreases activity [compare (1R,2S)-43 and (1R,2S)-30; Table 4].

The *in vitro* affinities of some compounds for striatal ^{3}H-spiroperidol and ^{3}H-NPA binding sites were determined. All compounds investigated had affinity for ^{3}H-NPA sites, whereas four of the compounds had affinity for ^{3}H-spiroperidol sites (Table 6).

In the series of C3-methylated 5-oxygenated 2-amino-tetralins, (2S,3R)-60 was inactive, whereas (2R,3S)-60, (2R,3R)-42 and (2S,3S)-42 seemed to be DA receptor agonists with actions on both pre- and postsynaptic receptors.

Compound (2R,3S)-60 (ED_{50}=5 nmol/kg) was shown to be a highly potent DA receptor agonist, equipotent to (2S)-5-OH-DPAT (ED_{50}≈4nmol/kg), whereas (2R,3R)-42 and (2S,3S)-42 seemed to be much less potent.

The dopaminergic effects of (2R)-5-OH-DPAT and (2S,3S)-42 may partially be due to contamination with the more potent enantiomers.

Racemic 61 was shown to have affinity for ^{3}H-NPA sites, but was inactive in the biochemical test in reserpinized rats (compare Tables 4 and 6). It should be noted that DA

receptor antagonists do not affect the DOPA accumulation in reserpinized rats. Thus, resolution of 61 and a pharmacological evaluation of the enantiomers may provide interesting results.

7.1.1 The DA D_2-receptor agonist conformation (Papers V-VI)

Due to the structural and pharmacological similarities between the DA agonists (R)-apomorphine, (4aS,10bS)-7-OHBQ [82,147], (2S)-5-OH-DPAT, (1S,2S)-41, (1R,2S)-43, (2R,3R)-42, and (2R,3S)-60 and the DA antagonists (S)-apomorphine [26-32] and (1S,2R)-43 it is reasonable to assume that they all bind to common receptor sites. This is significant since most DA antagonists differ considerably in structure from DA and probably interact with for example DA D_2-receptors by binding to accessory receptor areas. Thus, the present series of compounds offers a unique opportunity to obtain information about DA D_2-receptor topography.

Both (R)-apomorphine and (4aS,10bS)-7-OHBQ show high potency and stereoselectivity in their interaction with DA receptors [28,82]. It is established that (R)-apomorphine is a potent D_2-receptor agonist but the D_2-receptor affinity of (4aS,10bS)-7-OHBQ has not yet been determined. However, since these two compounds have similar pharmacological profiles *in vivo*, and since the 7,8-dihydroxy analogue of (4aS,10bS)-7-OHBQ is a potent D_2-receptor agonist [40], it is reasonable to assume that also the 7-hydroxy derivative is a D_2-receptor agonist.

(R)-Apomorphine and (4aS,10bS)-7-OHBQ are considerably more rigid than the 2-aminotetralins. Therefore, the computer generated best fit of the 2-aminotetralin moieties of (R)-apomorphine and (4aS,10bS)-7-OHBQ in their lowest energy conformations (Fig. 4) is highly informative. The fit is excellent and in fact, attempts to superimpose other conformations of the two compounds do not lead to a good fit as long as the electron pairs are included in the fitting procedure.

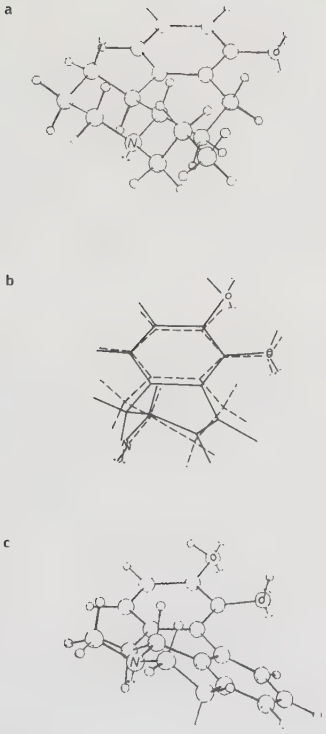


Figure 4. Computer generated fit (b) of the 2-aminotetralin fragments of the minimum energy conformations of (4a<u>S</u>,10b<u>S</u>)-7-OHBQ (a; dashed lines in b) and (<u>R</u>)-apomorphine (c; solid lines in b).

Thus, the fitted 2-aminotetralin fragments of (4a<u>S</u>,10b<u>S</u>)-7-OHBQ and (<u>R</u>)-apomorphine should be in "DA D_2-receptor agonistic conformations". These conformations have Φ-values around 0° and τ_N values around 60°. Similar conclusions have been reached previously by Kocjan and Hadzi [148] and by Tedesco <u>et al</u>. [54]. The possible importance of the N-electron pair (N-H) orientation for DA-receptor activation has been noted by several authors [42,54,149,150].

Conformations with Φ-values around 0° and τ_N-values around 60° are easily adopted by the DA D_2-receptor agonists 2S-5-OH-DPAT, (1R,2S)-43, and (2R,3S)-60 but in (1S,2S)-41, (2R,3R)-42, and in (2S)-61 such conformations are energetically disfavoured (see Table 3). In fact, attempts to minimize geometries of (1S,2S)-41 or (2R,3R)-42 with Φ-values around 0° and τ_N-values around 60° were unsuccessful; the minimization consistently changed either the tetralin ring conformation into Φ-values around 80° [(1S,2S)-41; Fig. 5] or the τ_N-value into 98° [(2R,3R)-42; Fig. 5].

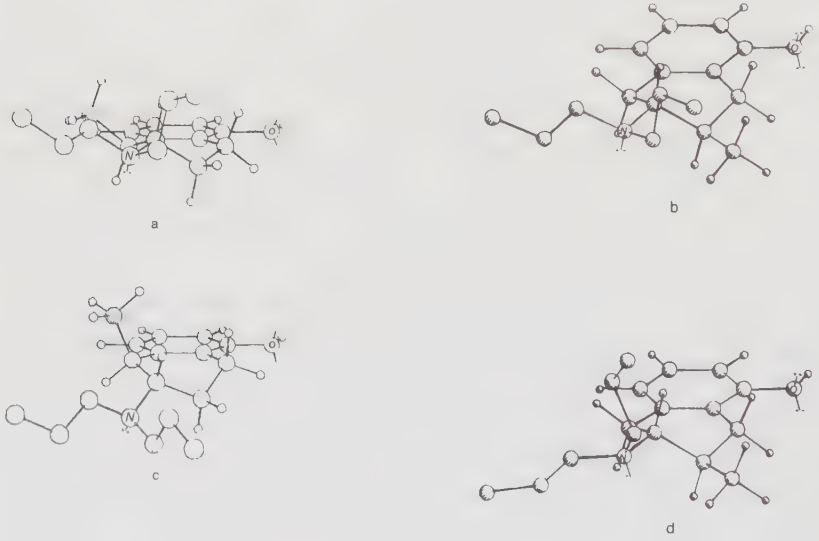
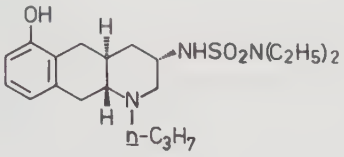


Figure 5. Starting geometries (a; Φ=0° and τ_N=60°; b; Φ=10° and τ_N=60°) and MMP2 minimized conformations (c; Φ=300° and τ_N=55°; d; Φ=10° and τ_N=98°) of (1S,2S)-41 and (2R,3R)-42, respectively.

These values are different from the "DA D_2-receptor agonistic 2-aminotetralin conformation". The reluctance of (1S,2S)-41 and (2R,3R)-42 to assume "agonist conformations" may provide an explanation for; (a) the low potency of (1S,2S)-41 as compared to (4aS,10bS)-7-OHBQ, which easily adopts an "agonist conformation" and (b) the low potency of

(2R,3R)-42 as compared to the potent dopaminergic (-)-N,N-diethyl-N'-[(3S,4aR,10bR)-1,2,3,4,4a,5,10,10b-octahydro-6-hydroxy-1-propyl-3-benzo[g]quinolinyl]sulfamide (70) [151,152] which contains the same structural elements as (2R,3R)-26.



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A pharmacological comparison of the DA D_2-receptor agonists (2S)-5-OH-DPAT, (1R,2S)-43 and (2R,3S)-60 shows that they differ considerably in potency. Compounds (2S)-5-OH-DPAT and (2R,3S)-60 are highly potent DA D_2-receptor agonists (ED_{50}'s≈4 nmol/kg and 5 nmol/kg, respectively), whereas the potency of (1R,2S)-43 (ED_{50}≈320 nmol/kg) appears to be several times lower. These compounds are all able to assume "DA D_2-receptor agonist conformations" ($\Phi \approx 0°$ and $\tau_N \approx 60°$, see Table 3) of low energy. The low potency of (1R,2S)-43 seems to be caused by the pseudoaxial C1-methyl group, which may have a negative influence on the receptor interaction (see Fig. 6). On the other hand, the pseudoaxial C3-methyl substituent in (2R,3S)-60 does not seem to provide sterical hindrance for the interaction with DA D_2-receptors, since (2R,3S)-60 is equipotent with (2S)-5-OH-DPAT.

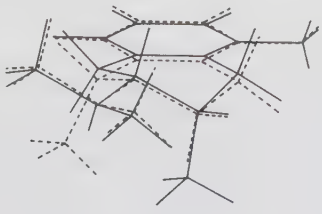


Figure 6. Computer generated fit of (1R,2S)-43 (dashed lines) and (2R,3S)-60 (solid lines) in their minimum energy conformations. For clarity, only the dimethylamino moieties are shown.

The absolute configurations at C2 of the homochiral (2R)-5-OH-DPAT, (1R,2R)-41, (2S,3S)-42, (1S,2R)-43 and (2S,3R)-60 make these compounds unable to assume "DA D_2-receptor agonistic nitrogen electron pair (N-H) orientations". This seems to be the main determinant for the low potency or inactivity of these compounds as DA receptor agonists.

Also the DA-receptor antagonists (1S,2R)-43, (S)-apomorphine, and (4aR,10bS)-7-OHBQ [150] are unable to assume "DA D_2-receptor agonistic nitrogen electron pair (N-H) orientations". However, the C1-methyl group of (1S,2R)-43, the nitrogen containing ring of (4aR,10bS)-7-OHBQ, and the nonhydroxylated aromatic ring of (S)-apomorphine may contribute favourably to D_2-affinity.

7.1.2 A partial DA D_2-receptor excluded volume (Papers IV-V)

The combination of the van der Waals volumes of the potent DA D_2-receptor agonists (R)-apomorphine, (4aS,10bS)-7-OHBQ, (2S)-5-OH-DPAT, and (2R,3S)-60 in their "DA D_2-receptor agonist conformations" should correspond to a partial "DA D_2-receptor excluded volume" (see Fig. 7; for definitions of receptor excluded volume and related concepts, see refs. 153 and 154).

7.2 C7-Oxygenated 2-aminotetralins (Paper VI)

The pharmacological results for some selected compounds are shown in Tables 4 and 5.

In this series of compounds, (1S,2R)-59 (ED_{50}≈65 nmol/kg) is the most potent DA receptor agonist, with actions on both pre- and postsynaptic receptors. However, it is about sevenfold less potent than (2R)-7-OH-DPAT (ED_{50}≈10 nmol/kg) [82]. As previously shown in the series of 5-oxygenated 2-aminotetralins (see Section 7.1 and ref. 46), both the N-n-propyl analogs and the methyl ethers are of lower potency than the N,N-di-n-propyl substituted phenols. In addition, compound (1S,2R)-59 appears to be a 5-HT receptor agonist of

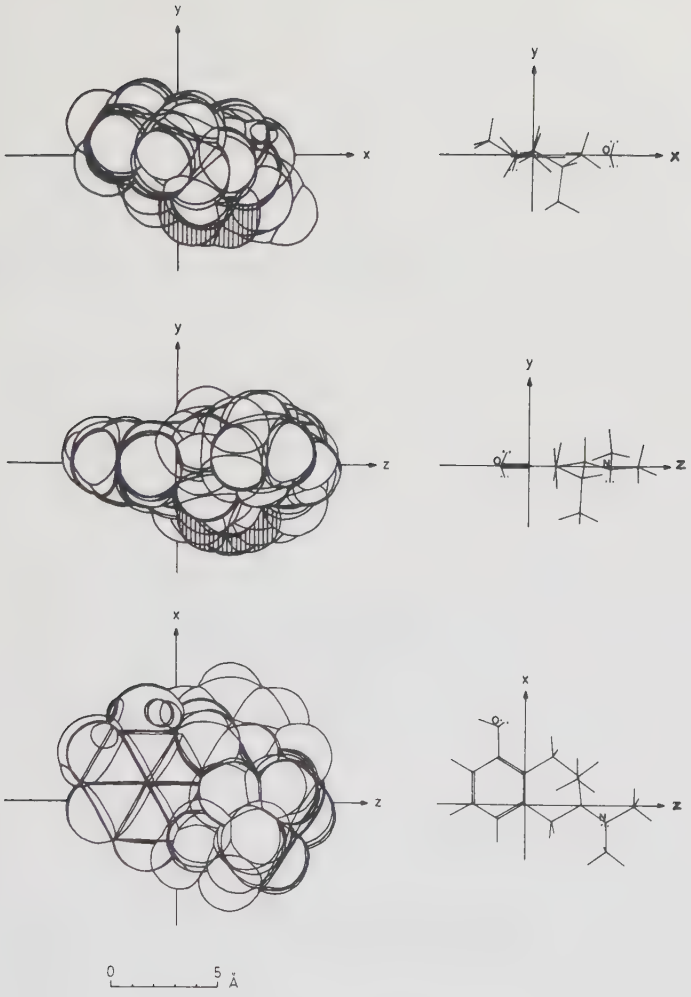
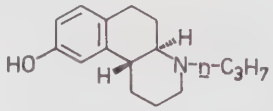


Figure 7. Partial "DA D_2-receptor excluded volume" (left), obtained by combination of (R)-apomorphine, the N-methyl derivative of (4aS,10bS)-7-OHBQ, and the N,N-dimethyl derivatives of (2S)-5-OH-DPAT and (2R,3S)-60 in their "agonist conformations". Three perspectives are shown, and each perspective of the coordinate system is defined to the right by insertion of the line projections of (2R,3S)-60. Dashed areas represent projections of the van der Waals volume of (2R,3S)-60 that exceeds the volume formed by combination of the other three compounds.

low potency (extrapolated ED_{50}≈4 μmol/kg). Compound (1R,2S)-59 is a considerably less potent DA receptor agonist than (1S,2R)-59. The dopaminergic effect of (1R,2S)-59 may be due to contamination of the more potent (1S,2R)-59. The trans-compound (1R,2R)-58 was inactive and (1S,2S)-58 and 62 did produce low locomotor activity in reserpinized rats but no other effects typical of DA receptor stimulation. The pharmacological profile of 63 is less defined; 63 induced a pronounced motor activity, consisting of tremor and irregular movements, in reserpinized rats and increased DOPA accumulation in non-pretreated rats.

7.2.1 The DA D_2-receptor agonist conformation (Paper VI)

A comparison of the "agonist conformation" of (2S)-5-OH-DPAT (Section 7.1.1) with the low energy conformations of (2R)-7-OH-DPAT by use of the concept of McDermed *et al.* [76,78,79], shows that the "agonist conformation" of 7-oxygenated 2-aminotetralins should correspond to Φ-values around 180° and τ_N-values around -60° (see Fig. 1). In fact, these values correspond to a low energy conformation of the more rigid and potent DA receptor agonist (4aR,10bR)-9-OHBQ [147,150].



(4aR,10bR)-9-OHBQ

The DA receptor agonist (1S,2R)-59 easily adopts low energy "agonist conformations" (see Table 3). In contrast, (1R,2R)-58, (1S,2S)-58, and 62 are unable to assume energetically accessible "DA D_2-receptor agonist conformations"; attempts to minimize "agonist conformations" of (1R,2R)-58 and (2S,3S)-62 were unsuccessful. The minimization changed the Φ-values [(1R,2R)-58] or the τ_N-values [(2S,3S)-62] into unfavourable values (compare 7.1.1). This may explain the inactivity of (1R,2R)-58 and the low activity/inactivity of 62.

The 2S-configuration of (1R,2S)-59 and (1S,2S)-58 makes these compounds unable to assume "DA D_2-receptor agonistic lone pair (N-H) orientations".

A comparison of (2R,3S)-60, which is the most potent DA receptor agonist of the C1-, C2- [137,138], and C3-methyl substituted 5-hydroxy-2-(di-n-propylamino)-tetralins, with (1S,2R)-59 reveals that both can assume energetically favourable "agonist conformations". When fitting such conformations of (1S,2R)-59 and (2R,3S)-60 according to the concept of McDermed *et al.* [76,78,79] (see Fig. 8), the pseudoaxial methyl groups become located close to each other and (1S,2R)-59 should fit well into the partial "DA D_2-receptor excluded volume" described in Section 7.1.2.

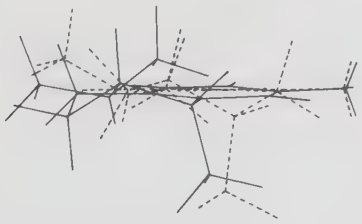


Figure 8. Computer generated fit of (1S,2R)-59 (solid lines) and (2R,3S)-60 (dashed lines) in their minimum energy conformations. For clarity, only the dimethylamino moieties are shown.

Racemic 63 increases DOPA accumulation in non-pretreated rats. This may indicate an antagonistic action of 63 at DA receptors. In addition, the structure of (2R,3S)-63 is similar to that of the previously described DA receptor antagonist (1S,2R)-43 (compare Fig. 9). However, 63 is a racemate and the final classification of the pharmacological profile has to be done by use of the enantiomers.

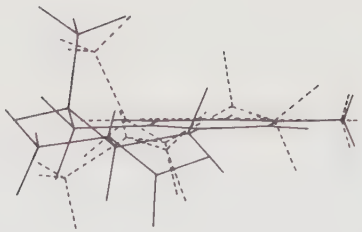
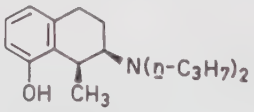


Figure 9. Computer generated fit of (1S,2R)-43 (dashed lines) and (2R,3S)-63 (solid lines) in their minimum energy conformations. For clarity, only the dimethylamino moieties are shown.

The *in vivo* biochemical data indicate that both enantiomers of 7-OH-DPAT may possess weak 5-HT receptor agonistic activity [155]. Also (1S,2R)-59 may be a 5-HT receptor agonist. In the 8-hydroxy-2-aminotetralin series, 8-OH-DPAT is weakly stereoselective [52,56,156] whereas the *cis*-C1-methylated derivative 71 is highly stereoselective [156,157]; (1S,2R)-71 is equipotent to 8-OH-DPAT whereas (1R,2S)-71 is inactive at 50 μmol/kg. A similar trend is observed here; both enantiomers of 7-OH-DPAT may be 5-HT agonists and only the (1S,2R)-enantiomer of 59 exhibits activity indicative of 5-HT receptor stimulation. In addition, *trans*-isomers 62, (1S,2S)-58, and (1R,2R)-58 and the *cis*-isomer 63 seem to be inactive as 5-HT agonists.



(1S,2R)-71

8 CONCLUSIONS

Introduction of methyl groups close to the N-bearing carbon of the potent DA D_2-receptor agonists 5-OH-DPAT and 7-OH-DPAT has given the following results:

* Compounds with novel pharmacological profiles of potential clinical value have been discovered.

* The low potencies of some derivatives that do not appear to present a "DA D_2-receptor essential volume" have led to a hypothesis about the "DA D_2-receptor active conformations" of 2-amino-5-hydroxytetralins and 2-amino-7-hydroxytetralins.

* The combination of the van der Waals volumes of the structurally related and potent DA D_2-receptor agonists (2R,3S)-60, (2S)-5-OH-DPAT, (R)-apomorphine, and (4aS,10bS)-7-OHBQ has allowed the definition of a partial "DA D_2-receptor excluded volume".

* This thesis has demonstrated the importance of using "optically pure" compounds with known absolute configuration in SAR-studies.

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